

The Role of Syndrome Differentiation in the Clinical Efficacy of *Punica granatum* on Patients with Ulcerative Colitis

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Abstract

Background: Tendency of patients toward diseases and their therapeutic responses are different based on their own temperament according to traditional Persian medicine.

Objectives: The aim of this study is to investigate the difference between therapeutic responses of hot and cold temperament patients (based on traditional Persian medicine) with ulcerative colitis to pomegranate peel extract.

Methods: Seventy-eight patients with moderate ulcerative colitis based on the Lichtiger colitis activity index (LCAI) criteria were randomized to receive an aqueous extract of the *Punica granatum* peel (6 grams per day) or placebo for four weeks. They were assessed before and after the intervention, in terms of symptoms, by the LCAI scoring system. The results were compared in two therapeutic groups based on the patients' temperament (cold and hot), which were diagnosed based on a previous validated questionnaire.

Results: Therapeutic response was significantly higher in patients with hot temperament compared to patients with cold temperament in the *P. granatum* group (1.916 ± 0.492 versus -0.500 ± 0.500 , $P = 0.029$).

Conclusions: This study showed the importance of considering syndrome differentiation and temperaments in interpreting the effect of *P. granatum* peels extract on ulcerative colitis.

Keywords: Punicaceae, Ulcerative Colitis, Traditional Medicine

1. Background

Patients with a unique disease, based on the current classification of diseases, may be classified in different types of diseases in the traditional medicine disease classification systems. These different traditional types need different therapeutic approaches. Applying these differences in researches on the efficacy of traditional medicine is called "syndrome differentiation". Syndrome differentiation can be applied in different levels of research protocol including intervention (assigning patients with different syndromes to different intervention groups) and analysis (comparing outcomes of patients with different syndromes and the same intervention).

Syndrome differentiation is applied frequently on traditional Chinese medicine researches (1). However, there are fewer reports on using this approach in traditional Persian medicine (TPM) researches. The temperament is an important concept for syndrome differentiation in Persian medicine (1-4). Patients, diseases and drugs are classified in Persian medicine into hot, cold, dry and wet tempera-

ments and each disease is treated through treatments with the opposite temperament (1). It should be kept in mind that these four basic qualities play a crucial role in different aspects of our lifestyle according to TPM measures (5, 6).

2. Objectives

Patients with ulcerative colitis are classified into hot and cold types based on the nature of causing humors in TPM. Pomegranate (*Punica granatum*) is a cold temperament fruit used for hot type ulcerative colitis in TPM. In this study, we aimed to investigate the potential difference between therapeutic responses of hot and cold temperament patients with ulcerative colitis to pomegranate peel extract.

3. Methods

A randomized double-blinded placebo-control clinical trial was conducted in a university affiliated gastroenterol-

ogy clinic. The inclusion criteria of this trial considered diagnosed ulcerative colitis patients (by a gastroenterologists) in the age bracket of 18 - 85 years old who had moderate disease severity according to the Lichtiger colitis activity index (LCAI). On the other hand, the exclusion criteria was: opium addiction, diabetes, pregnant and nursing women, any kind of sensitivity to pomegranate, 15 mg or more amount of daily consumption of prednisolone, anti-TNF agents and cyclosporine. In addition, patients with low levels of compliance and/or those confronting side effects were excluded too.

Seventy eight adult patients (18 - 65 years old) with moderate ulcerative colitis, based on the Lichtiger colitis activity index (LCAI) criteria (score of 4 - 11) at the Gastroenterology clinic of Isfahan University of Medical Sciences (Isfahan, Iran.) during January and June 2014, were randomized to receive an aqueous extract of the *Punica granatum* peel (6 gram per day) or placebo for four weeks as a complementary to standard medications based on a proposal approved by the ethics committee of Shahid Beheshti University of Medical Sciences and registered at the Iranian registry of clinical trials (IRCT2014040617156N1). Patients were assessed before and four weeks after the intervention in terms of symptoms by the LCAI scoring system. The results were compared in two therapeutic groups based on the patients' temperament (cold and hot) and diagnosed based on previous validated questionnaire (1). At the end, sixty-two patients completed the study.

3.1. Blindness and Randomization

Using random numbers generated by a computer, an equal randomization of patients into two groups of placebo and *P. granatum* was done. Regarding the concealment, not only the patients but also the investigators were not aware of the patients' allocation.

3.2. Instruments and Outcomes

Severity of ulcerative colitis was assessed by the means of LCAI. Moreover, as for the temperament evaluation, a new questionnaire based on the TPM concepts was used for temperament assessment in patients of both groups.

3.3. Sample Size Calculation

Considering 5% for type I and 20% for type II error in addition to the power of 0.8, sample size was calculated. Accordingly, 39 patients were considered for each group including a dropout rate of 20%. It is also to be noticed that all of the enrolled patients were from the city of Isfahan.

3.4. The Formula for Calculating Sample Size

Shedding more light on the methodology, the following Formula 1 was applied for sample size calculation.

$$n = \left(\frac{1 + \emptyset}{\emptyset} \right) \left[\frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2}{\Delta^2} \right] + \frac{Z_{1-\frac{\alpha}{2}}^2}{4} \quad (1)$$

3.5. Statistical Analysis

The results were compared in two therapeutic groups based on the patients' temperament (cold and hot) and diagnosed by the means of a previous validated questionnaire (7). Data analysis was done by application of the SPSS software version 16.0 (SPSS Inc., Chicago IL, USA). Kolmogorov-Smirnov test was used for the analysis of quantitative variables. Continuous and categorical data was reported as mean \pm standard deviation (SD) and number (percent).

4. Results

4.1. Participation Characteristics

A total number of 143 patients were assessed for the eligibility criteria during the months of January to June 2014. 78 patients enrolled in the study based on the inclusion criteria and amongst them, 62 participants finished the investigation.

4.2. Comparison of Demographic Data and Disease Characteristics Between the Groups

The mean age of 41.7 ± 10.9 and 37.8 ± 9.2 years were observed in case and placebo groups respectively. 16 males and 13 females in the case group versus 18 males and 15 females in the placebo group participated. The mean duration of the disease was 6.97 ± 7.36 years for the *P. granatum* group and 6.88 ± 5.33 years for the placebo group. Moreover, 17 patients in *P. granatum* and 21 patients in placebo group had left colitis in return of 12 participants, both in case and placebo groups with extended colitis. As for the drug consumption, all of the participants, i.e. 29 in case group and 33 in placebo group, were using 5-aminosalicylic acid (5-ASA). In addition, 5 people in the case group and 8 in placebo group were using immunosuppressive drugs while 7 in the case and 5 in placebo group reported to consume corticosteroids.

Patients in the *P. granatum* and placebo groups showed no significant difference in baseline demographic and clinical characteristics including age ($P = 0.126$), sex ($P = 0.999$), disease duration ($P = 0.501$), extension of colitis ($P = 0.796$) and medications: Immunosuppressive ($P = 0.548$) and corticosteroids ($P = 0.521$).

4.3. Effects of Intervention and the Role of Temperament in Therapeutic Response

Colitis activity index significantly reduced in both the *P. granatum* (6.34 ± 1.98 vs. 4.68 ± 1.92 , $P = 0.019$) and placebo (5.57 ± 1.75 vs. 4.51 ± 1.92 , $P = 0.002$) groups. Therapeutic response was higher in the *P. granatum* group compared with the placebo group, however, this difference was not statistically significant ($P = 0.555$).

Therapeutic response was significantly higher in patients with hot temperament compared to patients with cold temperament in the *P. granatum* group (1.916 ± 0.492 vs. -0.500 ± 0.500 , $P = 0.029$) (Figure 1), however, this difference was not significant in the placebo group ($P = 0.299$).

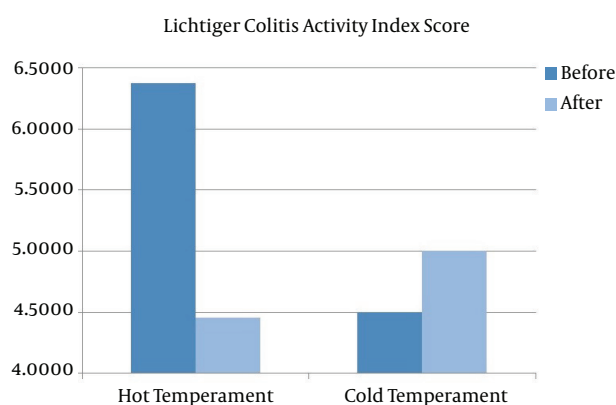


Figure 1. Comparison of Changes in the Lichtiger Colitis Activity Index Scores of Patients With Hot and Cold Temperaments in the *Punica granatum* Group

5. Discussion

This study showed different therapeutic responses of ulcerative colitis patients with different TPM temperaments to *P. granatum* peel extract. The results were compatible with the traditional medicine theory, which stated that patients with hot temperament had a better response to cold temperament remedies such as *P. granatum*.

Herbs with different temperaments based on TPM showed different effects on hormonal and metabolic parameters in previous studies (8). Different therapeutic responses of patients with ulcerative colitis with different traditional Chinese medicine syndromes were also documented previously (9). However, the effect of syndrome differentiation in the response of ulcerative colitis patients to TPM treatments was not investigated before this study. Different genotypes adhering to these temperamental phenotypes may be considered as a justifier of the observed effect, which should be investigated on more (10).

The effect of this formulation without comparing the response in different temperaments was reported previously (11).

As a conclusion, this study showed the importance of considering syndrome differentiation and temperaments in interpreting the effect of *P. granatum* peels extract on ulcerative colitis.

5.1. Limitations

Short duration of the intervention and small sample sizes were the most important limitations of this study. Moreover, considering the particular characteristics of the disease, only patients with moderate severity were included and severe cases were not considered.

5.2. Conclusions

In conclusion, this study revealed that there is an obvious relationship between the temperaments of the ulcerative colitis patients and their therapeutic response to *P. granatum* peels extract. It could be well understood when the concept of syndrome differentiation is considered.

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Footnotes

Authors' Contribution: All of the authors have participated equally in the present study.

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